Please add new claim 18 as follows:

18. A cell transfected with the viral vector of Claim 5.

REMARKS

This is responsive to the official action of October 15, 1997.

The Examiner has rejected Claims 1, 3-6, 8-11 and 15 under 35 USC 112 as being indefinite. This rejection is based upon the Examiner's assertion that "functionally equivalent", found in Claims 1 and 5, is vague and indefinite. The Applicants respectfully disagree. The Examiner is referred to the specification beginning at the second to last paragraph on page 2.

"p53as has been found to function as a growth regulator in all mammals tested regardless of whether or not p53as has been found to naturally occur in the mammal.

"It is to be understood that p53as may be of natural or synthetic form, provided that, at a minimum, terminal amino acids differ from the 50 terminal amino acids of p53 so that the modified products will act the same as active p53 protein and is functionally equivalent to mouse p53as protein.

"In general, it can be stated that p53as is functionally the same as p53 except that a p53as lacks the negative regulatory domain for p53 sequence specific DNA binding which is found within the last 50 amino acids at the p53 terminus. The negative regulatory domain of p53 negates p53 sequence specific binding in certain cellular environments which in turn causes p53 to lose activity. p53as lacks the negative regulatory domain and thus remains active in similar cellular environments."

From the above, it is clear that both p53 and p53as act as growth regulators mediated by sequence specific binding. Further it is clear that "active" means that the growth regulator function is in fact functioning, as opposed to "inactive", when it is not. There is no ambiguity.

The Examiner has also objected to the "encoded with Intron 10" language, although the Applicant's do not understand why. The Examiner is referred to page 3, line 11, which clearly refers to p53 as an Intron 10 sequence. This is simply a statement of a known state, i.e. everyone skilled in the art knows that the p53 nucleic acid sequence is found in Intron 10. The language has been removed from the claim since it is essentially a redundant and unnecessary characterization of what the designation "p53" is known to mean.

The Examiner has rejected Claim 15 on the ground that "at least a unique part" is not defined. The clear meaning of that terminology is that the part of the defined sequence in question must be unique, i.e. is not otherwise known and permits the raising of a polyclonal or monoclonal antibody. The claim has now been amended to include that understanding of unique. This is clearly supported on page 3, second paragraph of the specification.

The Examiner has rejected Claims 1 and 5 under 35 U.S.C.112 as containing subject matter which was not sufficiently described in the specification. The Applicants disagree.

There is in fact support for "active p53 encoded with intron 10" as previously discussed. However, since the specific language was not a necessary limitation in the claims, it has been deleted. The rejection is therefore moot. The "lacks" language suggested by the Examiner has been substituted for the "inactivates" language. That rejection has therefore also been rendered moot.

The Examiner has also objected to the claim language "so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as protein only." The Applicants respectfully disagree. The claim language is clearly supported.

The Examiner is referred to page 3, lines 6-7 of the specification which says: "To obtain a p53as the terminal amino acids of p53 are preferably modified, i.e., there is at least some substitution, as opposed to simple truncation." Further, beginning at the bottom of page 8 it is stated: "Further evidence for specificity of the p53as antibody is reactivity of anti-p53as with p53as but not with the major p53 protein." Details of antibody specificity for p53as and not for p53 are then given in several subsequent paragraphs. Since the modifications illustrated in the specification are at the C terminus, the claims have now been limited to that embodiment, i.e. p53 and p53as are defined as being sequentially identical up to the final 50 carboxy terminal amino acids of p53. The claims have thus been limited to the minimum difference between p53 and p53as defined on page 2, last paragraph

It is clearly taught that modification of the terminal amino acids of p53 can be used to eliminate the regulatory domain. Nothing further is required to enable one skilled in the art to do it. The advantages of a unique C terminus epitope are also clearly taught. Again, at the present state of the art, any genetic engineering lab technician could add such a unique epitope to the C terminus. A patent application is not supposed to be a textbook in well understood procedures. The teachings have been made of how to eliminate the negative regulatory domain of p53 by removing or altering the carboxy terminal sequence. Once this teaching is made, one of even menial skill in the art can do it Further, the desirability of incorporating a unique epitope is taught in the specification. Again, once this teaching is made, one of even menial

skill in the art can do it. It is the concepts, taught in the present application, of eliminating the negative regulatory domain and incorporating a unique epitope which is at the heart of the invention. Once these concepts are taught, one having only minimal skill can practice them since only well known standard procedures are needed. Certainly no undue experimentation is required or necessary.

Claims 1, 3, 4 and 15 have been rejected under 35 U.S.C. 102 as being anticipated by Wolf et al. as evidenced by Arai et al.

Claims 1, 3, 4 and 15 have been rejected as being anticipated by Arai et al.

At the outset, the 35 U.S.C. 102 rejection based upon a combination of Wolf et al. and Arai et al appears to be improper on its face. Anticipation by a combination of references is almost always improper unless one reference is being cited to show inherent properties of a disclosure of the other reference. That does not appear to be the case here. The rejection should be withdrawn (see MPEP 2131.01).

In any case both of the above rejections fall if Arai is not an anticipating reference. It is not such a reference as it does not meet many critical claim limitations.

The present claims require that p53as be functionally equivalent to active p53. The sequence disclosed by Arai et al and Wolf et al does not meet that very critical requirement.

The mutant p53 disclosed by Arai et al is not suggested by either Arai et al or Wolf et al as being active at all. Neither Arai et al nor Wolf et al suggest that the Arai et al sequence is present in normal cellular environments. Arai et al obtained his structure from chemically trans formed cells, not from normal cells. The amino acid sequence predicted (not prepared or isolated) by Arai et al and referred to by the Examiner, is not a p53as terminal sequence, but is

embedded. It would not be a separate peptide, even if translated (Translation is not suggested by Arai et al). Furthermore, the entire Arai et al sequence is not a p53as. The final nucleic acids of the encoding sequence of Arai et al simply do not match the encoding sequence of p53as of either naturally occurring p53 or naturally occurring p53as.

Please note that the mutant clone of Arai et al is distinct from p53 and p53as in structure and function. In structure, it has a mutation of the p53 gene coding region whereby a cyst residue at amino acid 132 is replaced by a phe residue. See Arai et al, 1986, page 3236 for entire coding sequence of p53-M-8 with the change noted. This alone is enough to prevent Arai et al from anticipating the present claims since the claims of the present application do not permit such an embedded variation. The pending claims require that the p53 and p53as sequences must be identical up to the carboxy terminus. This is necessary for p53as to retain p53 functionality. Arai et al and Wolf et al do not meet this requirement.

In function, the Arai et al (Wolf et al) M-8 mutant clone lacks the functionality of both p53 and p53as. This is completely contrary to the requirements of the present claims.

p53as has the properties of p53 including:

1. binding efficiently and specifically to the p53 consensus sequence in DNA and forming tetramers (see Kulesz-Martin et al.,Mol. Cell. Bio., pp 1698-1708, March 1994, and Wu et al., EMBO, Vol. 13, pp 4823-4830, 1994), and

2. transcriptional activation suppression of growth (Wu et al.,PNAS, pp 8982-8987, August 1997).

By contrast M-8 does not have the functionality of either p53 or p53as, but has its own deviant characteristics including:

1. transforming cells, rather than suppressing transformation (Eliyahu et al., Oncogene 3:313-321, 1998), and

2. forming monomers and dimers, not tetramers (Hainaut and Milner, EMBO 11:3513-3520, 1992).

Arai et al. (Wolf et al.) simply does not have a sequence which is the same as p53 up to the final 50 carboxy terminal amino acids, and does not have functionality similar to active p53 as required by the present claims. The Applicants have cited respected literature references showing these differences. In the absence of at least equally strong rebuttal evidence, the Examiner should withdraw these rejections. There is absolutely no reason or suggestion given by Arai et al or Wolf et al for incorporating a complete and functional p53as cDNA into a vector. Such a suggestion can only be obtained from the present Application by impermissible hindsight.

Claims 1, 3, 4 and 15 have been rejected under 35 U.S.C. 102 as being anticipated by Han et al.

This rejection should be withdrawn.

The Examiner has stated that Han incorporates p53 cDNA into a vector, either pGEM3z or pBluescript, citing page 1980 of Han et al. While the Examiner's confusion may be somewhat understandable, the Examiner is nevertheless in error. Han et al is interested in sequencing p53as cDNA and for that purpose only incorporates a p53as cDNA segment into a plasmid. The incorporated segment is only about one-third of a complete p53as cDNA. A whole p53as cDNA is never incorporated into a plasmid and in fact would be counterproductive for

Han et al's purposes. Large DNA fragments are difficult and sometimes impossible to sequence thus Han et al actually teaches against incorporating an entire p53as cDNA sequence.

Han et al does not incorporate p53as cDNA or any other functional p53 or p53as into anything. The Examiner's attention is called to column 2, page 1979 of Han et al under "Polymerase chain reaction..." where Han et al says: "3' p53 cDNA segment [RS4 9nt 1042 to 1539, +1 being the first nucleotide of the imitation codon ATG] was amplified by PCR..." (emphasis added). Han et al is trying to sequence p53as and in the process incorporates fragments into plasmids. The missing 1-1041 nucleotides from the incorporated RS4 segment renders the sequence inoperative as a sequence encoding a functional p53as. These first 1041 nucleotides, in fact, carry essential DNA binding information of p53as, thus their elimination makes any resulting translated peptide or protein useless as a functional p53as. Han et al. repeats the fact that only a 1042-1539 segment is used in column 2 under "RNase protection assay" referring to the RS4 segment noted above.

Han et al does not incorporate a p53as cDNA sequence into a plasmid or anything else, suggests no reason for incorporating such a sequence and because incorporating such a full sequence into a plasmid is counter productive to the characterization purposes of Han et al, actually teaches away from incorporating a p53as cDNA sequence into a plasmid. Han et al does not suggest that its incorporated p53 segment is biologically functional for any purpose, and in fact it is certainly not suitable for translation to a functional p53as protein.

Since Han et al does not incorporate a p53 cDNA sequence into any vector and suggests no reason for doing so, any rejection using this reference must necessarily use the teachings of

the present application for motivation to incorporate such a sequence. Such a rejection is therefore based upon impermissible hindsight.

The rejection based upon Han et al is therefore clearly improper and should be withdrawn.

The Examiner has rejected Claims 5, 6 and 8-11 under 35 U.S.C. 103 as being unpatentable over Wolf et al., Han et al., or Arai et al. in view of Lee et al.

This rejection is in error and should be withdrawn.

The basis for the Examiner's rejection is that "plasmid constructs of the p53as molecule were known in the art (Wolf et al., Arai et al., and Han et al.) and Lee et al. was cited to show that cloning of known sequences into baculoviral vectors was art standard technology. The premises of the rejection are faulty for several reasons. First of all, for the reasons previously discussed, none of Wolf et al., Arai et al. or Han et al. disclose plasmid constructs of the p53as molecule. Secondly, none of these references or their combination suggest any reason for making such a plasmid construct. And thirdly, even if such a suggestion were made, which it is not, it is a leap of logic with no documentary support, to say that placing a p53as cDNA sequence in a plasmid (with no reason given for doing so) makes it obvious to put such a sequence into a virus. The cited references must show more than technical feasibility. They must suggest a reason for engaging in the combining technology for the particular sequence in question. There are billions of things that are technically feasible but there is no reason to do them unless there is a reasonable end purpose. None of the cited references or their combination give such a purpose which can only be obtained from the present application by impermissible hindsight.

For the foregoing reasons all rejections should be withdrawn and all claims should be allowed.

Respectfully submitted,

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